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EXAMINER	
BRISTOL, LYNN ANNE	

ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
09/02/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/552,324	LOIBNER ET AL.	
	Examiner	Art Unit	
	LYNN BRISTOL	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 12-33* is/are pending in the application.

4a) Of the above claim(s) *4,6-8,10,14-28 and 33* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,9,12,13 and 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-10 and 12-33 are all the pending claims for this application.

2. Claims 1-10, 12-19, 22-28, and 30 are amended, Claim 11 is cancelled and new Claims 31-33 added by amendment in the Response of 4/10/08.

3. Claims 4, 6-8, 10, 14-28 and 33 are withdrawn from examination.

4. Claims 1-3, 5, 9, 12, 13, and 29-32 are all the pending claims under examination with species for a carbohydrate antigen (Lewis-Y, Sialyl-Tn and Globo H).

5. Applicants amendments have necessitated new grounds for objection and rejection. This action is FINAL.

Withdrawal of Objections

Specification

6. The objection to the text on pp. 9, 23, 24 of the specification for omitting the following symbols "□-Gal epitopes (Gal □ 1,3,Galβ1,4GlcNAc-R)", ""□-gal eptope" and "□1,3,Galactosyltransferse" (p. 9); "Maxisorp□" and "Novex□" (p. 23); and "□ 215 and □ 218 nm" (p. 24) is withdrawn in view of the replacement specification to correct these deficiencies.

7. The objection the specification for the improper use of trademarks, e.g., "Protein A Sepharose®", is withdrawn in view of the replacement specification to correct these errors.

8. The objection to the original specification for the improper layout under 37 CFR 1.77(b) is withdrawn in view of the replacement specification to correct the layout.

9. The objection to the figure legends for Figures 1-10 because they do not describe in brief but sufficient detail the data depicted in any of the figures is withdrawn in view of the replacement specification to correct these deficiencies.

10. The objection to Figures 2, 3 and 6-9 because the figures fail recite nucleic acid or protein sequence identifiers which are required under 37 CFR 1.821(c) is withdrawn. Applicants' submission of the drawings filed with the priority application WO 2004/091655 and containing the sequence identifiers for the figures is acknowledged. Additionally, upon further inspection of the file history, the examiner notes that the same set of drawings were filed upon national stage entry on 10/7/05. The examiner apologies for any inconvenience this may have caused applicants.

Claim Objections

11. The objections to Claims 5, 9, 12 and 30 are withdrawn for the following informalities:

a) Claims 5, 9 and 30 have been amended to bring the spelling for the carbohydrate "Lewis-y" into consistency.

b) Claim 12 has been amended to replace "CHI" with "CH1".

Withdrawal of Rejections

Claim Rejections - 35 USC § 112, second paragraph

12. The rejection of Claims 1-3, 5, 9, 11-13, 29 and 30 for the recitation “comprising at least a part of a murine IgG2a subtype amino acid sequence” in Claim 1 is withdrawn in view of the amendment of the claim to delete the phrase. However, the new amendment raises new grounds for rejection as discussed below.

13. The rejection of Claims 9, 11 and 12 in lacking antecedent basis for the limitation "the antigen" in Claim 9 is moot for cancelled Claim 11 and with drawn for Claim 9 in view of the amendment of the claim to depend from Claims 2 and 3.

14. The rejection of Claim 9 for reciting the phrase "such as" is withdrawn in view of the amendment of the claim to delete the phrase.

15. The rejection of Claim 9 for reciting improper Markush group language for the species “Lewis Y, Sialyl-Tn, Globo H” is withdrawn in view of the deletion of the species from the claim..

16. The rejection of Claim 12 for reciting improper Markush group language is withdrawn in view of the amendment of the claim.

17. The rejection of Claim 12 for the recitation "the IgG2a subtype amino acid sequence is contained in at least one of the regions selected from the CHI [*CH1*], hinge, CH2 and CH3 regions" is withdrawn in view of the amendment of the claim to depend from amended Claim 1 and to indicate that the sequence is inserted into the constant region of the antibody. However, the amendment of Claims 1 and 12 in responding to this rejection raises new grounds for rejection.

18. The rejection of Claim 30 for the recitation "said carbohydrate is *a number* selected from the group consisting of" is withdrawn in view of the amendment of the claim to replace the term "number" with "member."

Claim Rejections - 35 USC § 112, first paragraph

Enablement

19. The rejection of Claims 1-3, 5, 9, 11-13, 29 and 30 under 35 U.S.C. 112, first paragraph, in lacking enablement for any antibody comprising "at least part of a murine IgG2a subtype sequence" or an IgG1 antibody containing any part of a murine IgG2a subtype within the constant domain and still retain antigen binding and immunogenicity is withdrawn.

Applicants have amended Claim 1 to recite that the antibody is an IgG1 antibody having a constant region comprising a constant region of an IgG2 subtype amino acid sequence. The examiner's previous rejection was based on the ambiguity of the claims

which read on introducing the CDRs and frameworks of eh murine IgG2 antibody anywhere into the recombinant antibody.

Notably, the amendment of the claims raises new grounds for enablement as discussed below.

Claim Rejections - 35 USC § 102

20. The rejection of Claims 1-3 and 29 under 35 U.S.C. 102(b) as being anticipated by Hellstrom et al. (EP-A-0759442; published 2/26/97; cited in the IPER report enclosed with the filing of 10/7/05 and cited in the IDS of 8/22/07) is withdrawn.

Applicants' amendment of Claim 1 to introduce the subject matter of cancelled Claim 11 overcomes the rejection.

Claim Rejections - 35 USC § 102

21. The Claims 1-3, 5, 9 11-13, 29 and 30 under 35 U.S.C. 102(e) as being unpatentable over Eckert et al. (US 20050163768; published July 28, 2005; with priority to March 5, 2002 or earlier for the BR55-2 antibodies, BR55-2/IgG3 and BR55-2/IgG2) is withdrawn.

Applicants' amendment of Claim 1 to introduce the subject matter of cancelled Claim 11 overcomes the rejection.

Rejections Maintained

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. The rejection of Claims 2, 3, 5, 29 and 30 for the recitation ""or fragments thereof" in Claims 2 and 3 is maintained.

Applicants allege that the meaning is clear because only a fragment of tumor associated antigen may comprise an epitope or mimotope.

Response to Arguments

It is not clear if the limitation is referring to the antibody, the epitope or the tumor associated antigen of Claim 2; or the antibody, the mimitope or the tumor associated antigen of Claim 3. Antibody fragments are known in the art, a fragment of an epitope or minotope could be an aspect of the invention, and the tumor antigen could be a fragment.

23. The rejection of Claim 13 for the recitation "monoclonal antibodies produced by ATCC HB 9324 or ATCC HB 9347" because it is unclear how an antibody can be produced from an ATCC accession no. is maintained.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit

24. The rejection of Claim 13 under 35 U.S.C. § 112, first paragraph, because the specification does not provide evidence that the claimed hybridoma cell lines are (a) known and readily available to the public; (b) reproducible from the written description is maintained.

Applicants allege on pp. 10-11 of the Response of 4/10/08 that the same deposits were made in USPN 5,562,903 granted to the co-inventors Co and Loibner, and that the patent is granted to the present inventor. Applicants allege that the antibodies were well known in the art citing (WO 92/03165).

Response to Arguments

The instant application does not claim priority to USPN 5,562,903 or WO 92/03165 nor does the application incorporate the disclosures by reference with respect to the hybridomas.

A revised search of the ATCC website for the accession numbers, HB9324 and HB9347, did not identify there having been any deposits made under these accession nos. The USPN 5,562,903 issued on 10/8/96, and the release of the information would seemingly have occurred in the time frame since 1996.

Further, the only disclosure for the deposits appears on p. 15, lines 17-24 of the replacement specification of 4/10/08 where no description of the hybridomas is provided much less any relevant information on the repository and the date of deposit.

Absent a further showing that the deposits have actually been made, a suitable

deposit for patent purposes is now required. Applicants are also required to amend the instant specification to meet the requirements of the Budapest Treaty.

New Grounds for Objection

Specification/ New Matter

25. Applicants' amendment to the specification to cross-reference the instant application to the foreign priority application as an incorporation by reference is new matter. MPEP 201.03 G. Incorporation by Reference

**> An applicant may incorporate by reference the foreign priority application by including, in the U.S. application-as-filed, an explicit statement that such specifically enumerated foreign priority application or applications are "hereby incorporated by reference." The statement must appear in the specification. See 37 CFR 1.57(b) and MPEP § 608.01(p). For U.S. applications filed prior to September 21, 2004, the incorporation by reference statement may appear in the transmittal letter or in the specification."

Claim Objections

26. Claims 31 and 32 are objected to for reciting an apparent typographical error: the phrase "Globe H" should be amended to "Globo H."

New Grounds for Rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

27. Claims 1-3, 5, 9, 13, and 29-32 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) Claims 1-3, 5, 9, 13, and 29-32 are indefinite for the recitation "wherein a constant region of said IgG1 antibody comprises a constant region of an IgG2a subtype amino acid" in Claim 1 because it is unclear how a single "amino acid" can actually represent a region from the constant domain of the IgG2a antibody. Claim 1 could be amended to be consistent with Claim 12 where the phrase recites "an IgG2a subtype amino acid sequence."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

28. Claims 1-3, 5, 9, 12, 13, and 29-32 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an anti-idiotypic antibody for the Lewis-Y antigen where the recombinant IgG2a Le-Y antibody is an IgG2a hybrid designed for primate vaccination, which combines an anti-idiotyic Lewis-Y mimicking

herpervariable region and the highly immunogenic mouse IgG2a constant regions as shown in Figure 4, does not reasonably provide enablement for introducing any fragment of the constant region from an IgG2 antibody into the constant region of any IgG1 antibody in order to obtain a constant region comprising any hamster or primate glycosylation and being immunogenic in any primate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands, 8 USPQ2d 1400 (Fed. Cir.1988). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability of the art, the breadth of the claims, the quantity of experimentation which would be required in order to practice the invention as claimed.

Nature of the Invention

The claims encompass antibodies comprising any IgG2a subtype region from the constant domain cloned into the constant region an IgG1 antibody where the IgG2a comprises a hamster or primate glycosylation and the resultant recombinant antibody is designed for immunizing primates.

Disclosure in the Specification

The specification makes a general disclosure for anti-idiotypic antibodies against Lewis-Y (pp. 5, 12, 13, 14 and 36), Sialyl-Tn (p. 12) or Globo H (p. 12) carbohydrate

antigens. The specification discloses an anti-idiotypic antibody for the Lewis-Y antigen in Example 8 where the recombinant IgG2a Le-Y antibody is an IgG2a hybrid designed for primate vaccination, which combines an anti-idiotyic Lewis-Y mimicking herpervariable region and the highly immunogenic mouse IgG2a constant regions as shown in Figure 4. The immunogenicity is reported to be improved over the parent antibody, IGN301 wherein the anti-idiotypic antibody produces a strong IgG response against Lewis-Y expressing epithelial cancer cells. The antibody is expressed in HEK293 cells, transformed human embryonic kidney cell cultures so would result in primate glycosylation.

It is not well established in the art that an antibody encompassed by the claims is amenable to the extent and degree of the modifications to the Fc or constant domain that would allow proper folding and assembly of the antibody, and the specification is not any more enabling for producing a functional, immunogenic antibody that meets all of the claim limitations.

Prior Art Status: glycosylation of antibodies is unpredictable, dependent on the cell type and can affect antibody function.

It is known that not all cells glycosylate proteins in the same manner. As evidenced by Wright et al (Springer Semin Immunopathology ,15 :259-273 (1993)), while N-linked glycosylation is a wide spread post translational modification, occurring among mammalian, yeast, insect and plant cells, "the processing steps in the Golgi apparatus vary among cell types". (Page 259, second paragraph). Wright documents that plant cells use xylose, mammalian cells use sialic acid, and yeast add many more

mannose monomers than mammalian cells. Also insect cells do not appear to process the carbohydrates beyond the Man3 GLC Nac2 step. Accordingly, one skilled in the art would reasonably conclude that the tertiary structure of glycosylated antibodies, if actually glycosylated, which are encompassed by the broadly written claims would differ, based upon the teachings of Wright et al.

Further, Wright et al specifically teach that "the position of the carbohydrate addition appears to influence the structure of the added carbohydrate" (page 269, first full paragraph) and that "glycosylation can induce structural abnormalities in the light chain that lead to tissue deposition" (page 266-267, bridging paragraph). Finally, Wright et al teach that the sugars may fill “pockets" within the immunoglobulin , thus one of ordinary skill in the art would reasonably conclude that addition of carbohydrates to an antibody would alter the tertiary structure as evidenced from Delente (Trends in Biotechnology 3, letters to editor, No.9, (1985)) which teaches each glycosylated protein must be evaluated individually to determine the importance of glycosylation to its function and stability. Thus Wright et al teach the unpredictability of adding a glycosylation site to an antibody molecule, specifically that some additions result in protein aggregation; that the position of the addition is important for determining whether the glycosylation site is in fact recognized by the cell; and once glycosylated, whether the antibody is more or less stable and binds antigen like the unaltered form. One skilled in the art would also reasonably conclude from Wright et al that glycosylation in the CH1 or constant K (CK) region could have similar structural effects as those in the light chain mentioned above.

As evidenced by Olden et al (Biochem et Biophys Acta 650:209-232 (1982)), carbohydrate structures are a form of sorting signals used by the cells and that O-linked glycosylation differ from N-linked glycosylation due to the sugars which are added to each type during protein processing. O-linked carbohydrates use galNAC while N-linked carbohydrates use GlcNAC (see page 225, second column, first paragraph). Olden teaches that O-linked carbohydrates differ in tertiary structure from N-linked carbohydrates and therefore, one skilled in the art would reasonably conclude that antibodies possessing O-linked sugars would also differ in their tertiary structure from those antibodies expressing N-linked sugars.

Moreover, while the N-linked carbohydrate addition site is specifically the sequence "ASP-X-SER/THR, where X may stand for any amino acid, the O-linked addition site is less defined as only a serine or a threonine residue. Carbohydrate moieties are not attached to all lumenal serine or threonine residues and it would be unpredictable to determine at which lumenal positions a serine or a threonine could be placed within the antibody molecule so that the serine or threonine would be glycosylated. Once glycosylated, whether by the N-linked or O-linked mechanism, it would require undue experimentation to determine whether the antibody expression, stability, tertiary structure or affinity had been affected.

Since the state of the art of protein modification suggests that the effects of sequence alterations are unpredictable, and furthermore, as evidenced by Wright et al, Delente, and Olden et al concerning the unpredictability of adding carbohydrates to antibodies and since the specification provides inadequate guidance as to which

constant domain changes would result in hamster or primate glycosylation and a functional antibody, wherein the glycosylation site is actually used, and the antibody stability/function is not reduced, undue experimentation would be required to determine which IgG2 constant domain regions would result in the hamster- or primate-glycosylated antibody molecule that could still be bind its antigen and would be used to immunize primates.

Prior Art Status: Modifications to the Heavy Chain Constant Regions are Unpredictable

The claims encompass antibodies comprising modified constant regions and are not limited to the domain substitutions. The claims do not specify whether the hinge, CH1, CH2 or CH3 domains are substituted or where the substitutions would take place. It is well accepted in the art that the constant region contributes to flexibility, half-life and the effector functions of an antibody.

Salfeld (Nature Biotech. 25(12): 1369-1372 (2007)) describes some of the properties for the IgG isotype constant regions in Table 1 and suggests that the constant region can be modified based on the intended effector functions but that results can vary depending on which domain and how the domain is mutagenized (p. 1371, Col. 2, ¶2-3).

The state of the art at the time the invention was made recognized that even single amino acid differences can result in drastically altered function of antibodies. For example, Lund et al. (The Journal of Immunology 1996, 157:4963-4969) show that even a single amino acid replacement within the CH2 domain of IgG can alter the

glycosylation profile of an antibody therefore influence its effector functions of Fc receptor binding and complement activation (see entire document, particularly Discussion on pages 4966-4968). Further, Lazar et al. (WO 03/074679) teach that the determinants of antibody properties, such as stability, solubility and affinity for antigen, important to its functions are overlapping; thus engineering an Fc region of an antibody may cause a loss in affinity for its antigen (see entire document, particularly page 3).

Given the extensive variation permitted by the instant claim language, the skilled artisan would not reasonably predict the combination of which IgG2 constant domain region, for example, CH1, hinge, CH2, CH3, and CH4 much less the CL have the same function as the instant claimed invention. Reasonable correlation must exist between the scope of the claims and scope to enablement set forth.

The specification does not appear to provide sufficient guidance as to which constant domains should or should not be changed to preserve any particular function. The variation permitted by the instant claim language is extensive. There does not appear to be sufficient guidance in the specification as filed as to how the skilled artisan would make and use the claimed recombinant antibody.

Therefore, in view of the lack of guidance in the specification and in view of the unpredictability in the art of glycosylation of proteins as evidenced by Wright et al, Olden et al, and Delente and the unpredictability of glycosylation of antibodies as evidenced by the specification, one of skill in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Conclusion

29. No claims are allowed.

30. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

31. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lynn Bristol whose telephone number is 571-272-6883. The examiner can normally be reached on 8:00-4:00, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

LAB

/David J Blanchard/
Primary Examiner, Art Unit 1643